Mini review

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Khat a drug of abuse: roles of free radicals and antioxidants‡

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Many articles have reviewed the health impact of Khat consumption; however the role of free radicals in the pathogenesis associated with short- and long-term consumption of Khat is absent in the literature. As free radicals and antioxidants converge across various mechanisms in normal physiological function and in disease, this review attempts to uncover the role of endogenous free radicals and the mechanism of cellular injury associated with Khat consumption.

Keywords: Khat; free radicals; reactive oxygen species; reactive nitrogen species; cellular damage; liver; superoxide

Introduction

Khat or Catha Edulis is a natural stimulant that is grown successfully in Ethiopia, Kenya, Djibouti, and Yemen, often at the expense of food crops due to its adaptability to various harsh and challenging environments. Khat dependency is believed to be much less than amphetamine, a drug with similar structure and more potency. In a report from the 34th WHO Expert Committee on Drug Dependence,[1] Khat dependency data were reviewed and the Committee recommended that Khat should not be internationally controlled. In its report, the Committee felt that an educational campaign must be conducted to inform about the many health effects associated with excessive consumption. The following sections discuss the scientific evidence and knowledge regarding the cellular damage associated with Khat consumption.

Khat and oxidative stress

Oxidative stress occurs when there is an imbalance between the toxic effect of oxidants and the protection of the antioxidant defence system. The hallmark of oxidative stress is an increase in the production of reactive nitrogen species (RNS) and reactive oxygen species (ROS), such as nitric oxide (NO^-), the superoxide anion (O_2^-), hydroxyl radicals ($OH^\bullet$) and peroxinitrite ($ONOO^-$) (Figure 1). Enzymatic and non-enzymatic antioxidant defence mechanisms in the human body protect it from damage and maintain biological functions at optimal levels. These powerful antioxidant systems include superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px). The most abundant thiol antioxidant in mammalian cells is glutathione (GSH), which functions through the glutathione redox system. Antioxidants quench free radicals and protect against oxidative damage, maintaining redox equilibrium. However, the depletion of the antioxidant system causes a cascade of reactions that result in cell damage and enzyme inhibition.

Khat has recently been found to induce oxidative stress in humans.[2] Our published studies have shown that long-term Khat abusers have higher levels of free radicals in their blood. Consumption of Khat for a period of over 12 months, at a minimum frequency of once per week, resulted in an increase in free radicals in the plasma of chronic Khat abusers when compared to control subjects (abstainers). The high levels of free radicals could be linked directly to the effects of the Khat constituents cathine and cathinone, or indirectly through the exposure of Khat to pesticides during or after cultivation. The high levels of free radicals could result in the inhibition of multiple antioxidant enzymes responsible for scavenging these radicals. In the same report[2] we investigated the presence of pesticides in Khat by measuring cholinesterase activity in the plasma of Khat users. Decreased cholinesterase activity indicated that the pesticides in Khat leaves were implicated as the causal factor of increased amounts of free radicals. It was revealed for the first time that Khat may contribute to a high oxidative stress burden in humans.[2]

The mechanism by which Khat or its constituents generate free radicals is still largely unknown. Recent studies have shown that Khat consumption in rats leads to free radical formation and affects the antioxidant system. In a report by Al-qirim,[3] it was suggested that Khat toxicity is due to the reduction in the activity of the free radical scavenging/metabolizing enzymes superoxide dismutase (SOD, catalase (CAT) and glutathione-*S*-transferase (GST), and that this effect is caused by the alkaloid constituents of Khat when these are administered orally. By contrast, when rats were treated with the flavonoid fraction of Khat, an enhancement in antioxidant activity was observed and SOD was not affected by this treatment. Flavonoids possess high superoxide dismutase activity, which could explain why there was no change observed in this group. Flavonoids are a group of compounds that have

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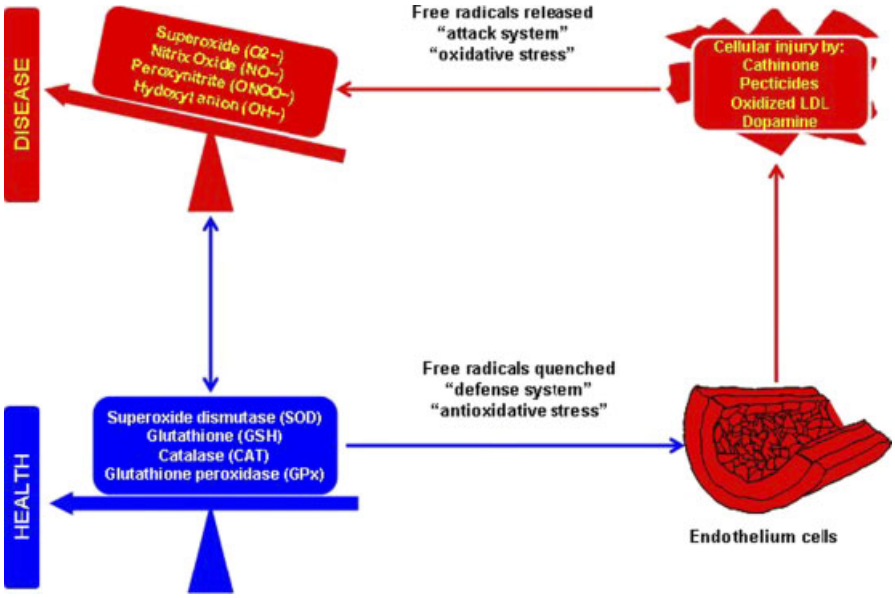

Figure 1. When cellular injury occurs as a result of chemical or biological insults by cathinone, pesticides, oxidized LDL or metabolites of oxidized dopamine, free radicals [the attack system] are generated. Superoxide (O_2-), nitric oxide (NO–), peroxyinitrite (ONOO–) and hydroxyl anion (OH–) attack endothelial cells lining the vascular wall causing cell death (disease]. Antioxidative stress enzymes and protein molecules responding to oxidative stress quench free radicals that can contribute to oxidative stress and restore free radicals balance [health]. Antioxidants enzymes like superoxide dismutase (SOD) convert highly reactive and damaging superoxide to hydrogen peroxides (H_2O_2) that are less reactive than superoxide. Catalase (CAT) catalyzes the decomposition of H_2O_2 to water and oxygen. Glutathione (GSH) removes toxic metabolites created by reactive oxygen species (ROS). Glutathione peroxidase (GPx), removes peroxides (i.e. lipid peroxide) using the GSH as a reducing agent. GSH is then reduced back to GSH by glutathione reductase (GSR).

antiviral, anti-inflammatory, and antioxidant activities. Thousands of flavonoids have been isolated and identified in vegetables and fruit[4] including quercetin, isoxanthohumol, and genistein, which act as free radical chain reaction terminators.

Khat and blood-brain barrier dysfunction

The blood-brain barrier (BBB) is protected from the invasion of blood-born chemicals by a group of xenobiotic metabolizing enzymes that resemble the liver enzymes involved in drug metabolism, but possess lower enzymatic activity levels. Inflammation and microvascular dysfunction occurring at the tight junctions of the BBB are accompanied by an increase in ROS and RNS that is associated with BBB dysfunction. BBB dysfunction causes an increase in its permeability, which correlates with the development of neuro-inflammatory diseases like multiple sclerosis, dementia, stroke, and brain trauma.[5] This increased permeability is accompanied by changes in the structure and localization of the intracellular tight junction (TJ) protein occludin. During oxidative stress, occludin moves away from the TJ.[6] Recent studies have demonstrated that Khat consumption results in morphological changes in the cerebral cortex of early postnatal rats compared to older ones. This might explain recent findings suggesting that ROS are formed during hypoxia and re-oxygenation, and lead to an increased permeability of the BBB. There are reports of increased numbers of sudden deaths among Khat abusers in Yemen during or shortly after Khat sessions (Aleryani, unpublished data). There is at least one report of a myocardial ischemia-reperfusion injury following ingestion. It is implied that oxidative stress could cause endothelial dysfunction and artherogenesis.[7]

Khat and glutathione depletion

GSH is one of the most abundant physiological antioxidants in mammalian cells and is found in almost every organ and cellular system. GSH plays a major role in protecting cells from oxidative injury. GSH depletion is associated with pathological conditions such as depletion-induced chromosomal DNA fragmentation, cystic fibrosis, and cataract.[8–10] The presence of thiol groups indicates the capacity to undergo redox reactions. For example, when nitric oxide (NO) levels are increased during oxidative stress injury (Figure 1), the thiol group serves as scavenger by 'storing' NO. The newly formed compound, nitrosoglutathione (GSNO), circulates in the serum and prevents NO from participating in further oxidative stress reactions.[11] A recent report described free radical formation and GSH depletion as possible early causes of Khat cytotoxicity.[12]

Khat and apoptosis

Under normal physiological conditions, Khat consumption induces oxidative stress.[2] During this process, the antioxidant capacity of the system could be exhausted and trigger programmed cell death, which can be induced by reactive oxygen species. Khat has been reported to induce cell death and apoptosis in leukaemia cell lines within two hours of exposure.[12] Khat has also been found to induce apoptosis and trigger the generation of free radicals in normal human oral keratinocytes and fibroblasts.[13]

Khat and neurotoxicity

Khat has been found to increase dopamine (DA) release from the striatum and nucleus accumbens. The oxidative metabolism of

DA leads to the generation of free radicals and an increase in the synthesis of reactive oxygen and nitrogen species. The formation of free radicals is associated with neuronal degeneration.[14]

Khat and antioxidants

Antioxidants are important in health due to their capacity to scavenge reactive oxygen species. In a report by Farag *et al*.,[15] intragastric administration of Khat in adult rabbits resulted in lower GSH levels compared to controls. This finding was in agreement with the findings of Al-Zubairi *et al*.,[16] who reported low levels of malondialdehyde (MDA), a marker for lipid peroxidation, in the sera of post-meal human male Khat chewers. The absence of lipid peroxidation in this group does not exclude the toxic effect and production of free radicals by Khat. It is possible that the presence of tannins, which are known antioxidants, was responsible for this effect.[17] In a recent report, Khat was shown to cause mitochondrial dysfunction and excessive production of reactive oxygen species.[18]

Conclusions

In conclusion, a growing body of evidence implicates oxygen-derived free radicals in disease development of neurodegeneration, cognitive impairment, and psychosis.[19–22] Recently, Khat has been found to be a risk factor for psychotic disorders,[23] especially with excessive Khat consumption. Cognitive impairment, the clinical precursor of Alzheimer's disease, is characterized by elevations in oxidative stress.[24] Khat has been recognized as a precipitant of psychosis and has also been reported to cause cognitive impairment.[25]

The effect of oxidative injury has been recently implicated in the pathophysiology of schizophrenia.[26–28] In addition, cellular DNA damage levels caused by free radicals are increased in schizophrenic patients compared to healthy subjects.[29] The evidence that free radicals contribute to antioxidants enzymes inhibitions may contribute to the changes in neurons membrane phospholipids and fatty acids alterations.[30–31] There is great interest in assessing Khat toxic effects on free radicals generation and oxidative stress in humans. Khat research in this area could increase our knowledge and establish links between Khat consumption and mental disorders.

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